44109.(Amended) The kit of Claim ~~108~~ 43, wherein the agonist is NS-1619, 1-EBIO, a guanylyl cyclase activator, a guanylyl cyclase activating protein, minoxidil, pinacidil, cromakalim, or levcromakalim.

E15 Ont

REMARKS

The amendments to the specification submitted herein are to correct obvious typographical errors.

The amendments to Claims 1, 4, 9, 11-18, 21, 26, 28-34, 97, 100, 104, 108, and 109, submitted herein were suggested by Examiner Baker in a telephonic interview she graciously granted on July 25, 2002. These amendments are merely cosmetic and for the sake of greater clarity, and they do not relate to issues of patentability.

Applicant will file next week a petition to accept color photographs and two additional copies of the color photographs, as required by Examiner Baker in the interview.

CONCLUSION

In view of the above amendments and remarks, it is submitted that this application is now ready for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney at (213) 896-6665.

Respectfully submitted,

By: Nisan A. Steinberg, Ph.D.
Reg. No. 40,345

SIDLEY AUSTIN BROWN & WOOD
555 West Fifth Street, Suite 4000
Los Angeles, California 90013
Ofc: 213/ 896-6665
Fax: 213/ 896-6600
23066.1

C:\NRPORTBL\LA1\NSTEINBF\443181_1.DOC

35

Version With Markings to Show Changes Made

Deletions are indicated with bold brackets to distinguish them from brackets that are part of the desired text.

In the Specification:

Please delete the paragraph at page 4, lines 6-11, and insert therefor the following:

--Intracarotid infusion of leukotriene C.sub.4 (LTC_4[.sub.4]) selectively increases the permeability in brain tumor capillaries without affecting the permeability in normal brain capillaries. The effect of LTC_4[.sub.4] on brain tumor capillaries is, however, limited to small molecules and it can only slightly increase the permeability of those small molecules in abnormal brain tissue relative to normal. Accordingly, LTC_4[.sub.4] does not significantly increase the delivery of some larger water soluble molecules to brain tumors or other abnormalities.--.

Please delete the paragraph at page 4, lines 12-28, and insert therefor the following:

--The vasoactive n[a]onopeptide bradykinin and agonists or polypeptide analogs thereof (e.g., receptor-mediated permeabilizers [RMPs]) have been injected intravenously to increase blood-brain barrier permeability to co-administered neuropharmaceutical or diagnostic agents. (B. Malfroy-Camine, *Method for increasing blood-brain barrier permeability by administering a bradykinin agonist of blood-brain barrier permeability*, U.S. Patent No. 5,112,596; J.W. Kozarich *et al.*, *Increasing blood brain barrier permeability with permeabilizer peptides*, U.S. Patent No. 5,268,164). Intracarotid infusion of bradykinin will selectively increase permeability 2- to 12-fold in brain tumor and ischemic brain capillaries for molecules ranging in molecular weight from 100 to 70,000 Daltons (Inamura, T. *et a l.*, Bradykinin selectively opens blood-tumor barrier in experimental brain tumors, J. Cereb. Blood Flow Metab. 14(5):862-70 [1994]). Bradykinin does not increase permeability in the normal blood brain barrier except at very high

doses. (Wirth, K. *et al.*, *DesArg9-D-Arg[Hyp3,Thi5,D-Tic7,Oic8]bradykinin (desArg10-[Hoe140]) is a potent bradykinin B1 receptor antagonist*, Eur. J. Pharmacol. 205(2):217-18 [1991]). Opening of the blood-tumor barrier by bradykinin is transient, lasting 15 to 20 minutes. (Inamura *et al.* [1994]). After opening of abnormal brain capillaries with bradykinin, the capillaries become refractory to the bradykinin effect for up to 60 minutes. (Inamura *et al.* [1994]).--.

Please delete the paragraph at page 11, lines 4-11, and insert therefor the following:

--However, the potassium channel agonist employed in the inventive methods is one other than the vasodilator bradykinin (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg), or a polypeptide bradykinin analog, such as receptor mediated permeabilizer (RMP)-7 or A7 (e.g., Kozarich *et al.*, U.S. Patent No. 5,268,164 and PCT Application No. WO 92/18529). Other analogs of bradykinin include related peptide structures which exhibit the same properties as bradykinin but have modified amino acids or peptide extensions on either terminal end of the peptide. Examples of bradykinin analogs include [phe^{8}[.sup.8] (CH_2[.sub.2]–NH) Arg^{9}[.sup.9]-bradykinin, N–acetyl [phe^{8}[.sup.8] (CH_2[.sub.2]--NH--Arg^{9}[.sup.9]] bradykinin and desArg9-bradykinin.--.

Please delete the paragraph at page 18, lines 21-25, and insert therefor the following:

--The dose-dependent nature of this increased permeability is demonstrated in Figure 2, which shows that increasing the dose of NS-1619 results in an increase in the unidirectional transfer constant K_i for [^{14}C]α-aminoisobutyric acid in RG2 glioma capillaries. At higher doses (100 and 110 μg/kg/min) a significant drop in the arterial blood pressure of the rats was observed. The numbers of rats used in each group is shown in parentheses in Figure[s] 2.--.

In the Claims:

Please amend Claims 1, 4, 9, 11-18, 21, 26, 28-34, 97, 100, 104, 108, and 109, as follows.

1. (Twice Amended) A method of delivering a medicant to an abnormal brain region in a mammalian subject, comprising:

administering to a mammalian subject having an abnormal brain region an [potassium channel] agonist of a calcium-activated or ATP-sensitive potassium channel, [said potassium channel] the agonist being other than bradykinin or a bradykinin analog, under conditions and in an amount sufficient to increase the permeability to the medicant of a capillary or arteriole delivering blood to cells of the abnormal brain region; and

administering to the subject simultaneously or substantially simultaneously with the [potassium channel] agonist the medicant, so that the medicant is delivered selectively to the cells of the abnormal brain region compared to normal brain regions.

4.(Amended) The method of Claim 1, wherein the [potassium channel] agonist is NS-1619, 1-EBIO, a guanylyl cyclase activator, a guanylyl cyclase activating protein, minoxidil, pinacidil, cromakalim, or levcromakalim.

9.(Amended) The method of Claim 1, wherein the medicant is a N-methyl-D-aspartate (NMDA) receptor antagonist, antibiotic, interleukin-2,[; or] transforming growth factor-β, cisplatin, carboplatin, tumor necrosis factor-α, methotrexate, 5-fluorouracil, amphotericin, daunorubicin, doxorubicin, vincristine, vinblastine, busulfan, chlorambucil, cyclophosphamide, melphalan, or ethyl ethanesulfonic acid.

11.(Amended) The method of Claim 1, wherein administering the [potassium channel] agonist is by intravenous or intra-arterial infusion or injection.

12.(Amended) The method of Claim 1, wherein administering the [potassium channel]

agonist is by intracarotid infusion or injection.

13.(Amended) The method of Claim 1, wherein the [potassium channel] agonist is administered to the mammalian subject by a bolus injection.

14.(Amended) The method of Claim 1, wherein the [potassium channel] agonist is administered to the mammalian subject in an amount from about 0.075 to 1500 micrograms per kilogram body mass.

15.(Amended) The method of Claim 14, wherein the [potassium channel] agonist is administered to the subject in an amount from about 0.075 to 150 micrograms per kilogram body mass.

16.(Amended) The method of Claim 1, wherein the [potassium channel] agonist is administered to the mammalian subject at a dose rate of about 0.075 to about 100 $\mu g\ kg^{-1}\ min^{-1}$ for up to about 30 minutes.

17.(Amended) The method of Claim 16, wherein the [potassium channel] agonist is administered to the mammalian subject at a dose rate of about 0.075 to about 15 $\mu g\ kg^{-1}\ min^{-1}$.

18. (Twice Amended) A method of selectively delivering a medicant to an abnormal brain region in a mammalian subject, comprising:

administering to a mammalian subject having an abnormal brain region an [potassium channel] agonist of a calcium-activated or ATP-sensitive potassium channel, [said potassium channel] the agonist being other than bradykinin or a bradykinin analog, under conditions and in an amount sufficient to increase potassium flux through a calcium-activated or ATP-sensitive potassium channel in an endothelial cell membrane of a capillary or arteriole delivering blood to cells of the abnormal brain region, whereby the capillary or arteriole is made more permeable to the medicant; and

administering to the subject simultaneously or substantially simultaneously with the [potassium channel] agonist the medicant, so that the medicant is delivered selectively to the cells of the abnormal brain region compared to normal brain regions.

21.(Amended) The method of Claim 18, wherein the [potassium channel] agonist is NS-1619, 1-EBIO, a guanylyl cyclase activator, a guanylyl cyclase activating protein, minoxidil, pinacidil, cromakalim, or levcromakalim.

26.(Amended) The method of Claim 18, wherein the medicant is a N-methyl-D-aspartate (NMDA) receptor antagonist, antibiotic, interleukin-2,[; or] transforming growth factor-β, cisplatin, carboplatin, tumor necrosis factor-α, methotrexate, 5-fluorouracil, amphotericin, daunorubicin, doxorubicin, vincristine, vinblastine, busulfan, chlorambucil, cyclophosphamide, melphalan, or ethyl ethanesulfonic acid.

28.(Amended) The method of Claim 18, wherein administering the [potassium channel] agonist is by intravenous or intra-arterial infusion or injection.

29.(Amended) The method of Claim 18, wherein administering the [potassium channel] agonist is by intracarotid infusion or injection.

30.(Amended) The method of Claim 18, wherein the [potassium channel] agonist is administered to the mammalian subject by a bolus injection.

31.(Amended) The method of Claim 18, wherein the [potassium channel] agonist is administered to the mammalian subject in an amount from about 0.075 to 1500 micrograms per kilogram body mass.

32.(Amended) The method of Claim 31, wherein the [potassium channel] agonist is administered to the subject in an amount from about 0.075 to 150 micrograms per kilogram

body mass.

33.(Amended) The method of Claim 18, wherein the [potassium channel] agonist is administered to the mammalian subject at a dose rate of about 0.075 to about 100 $\mu g\ kg^{-1}\ min^{-1}$ for up to about 30 minutes.

34.(Amended) The method of Claim 33, wherein the [potassium channel] agonist is administered to the mammalian subject at a dose rate of about 0.075 to about 15 $\mu g\ kg^{-1}\ min^{-1}$.

97. (Twice Amended) A pharmaceutical composition comprising a combination of an [potassium channel] agonist of a calcium-activated or ATP-sensitive potassium channel, [said potassium channel] the agonist being other than bradykinin or a bradykinin analog, formulated in a pharmaceutically acceptable solution together with a medicant for delivery by intravascular infusion or injection into a mammal.

100.(Amended) The pharmaceutical composition of Claim 97, wherein the [potassium channel] agonist is NS-1619, 1-EBIO, a guanylyl cyclase activator, a guanylyl cyclase activating protein, minoxidil, pinacidil, cromakalim, or levcromakalim.

104.(Twice Amended) The pharmaceutical composition of Claim 97, wherein the medicant is a N–methyl-D-aspartate (NMDA) receptor antagonist, antibiotic, interleukin-2,[;]or transforming growth factor-β.

108. (Thrice Amended) A kit for enhancing the delivery of a medicant to an abnormal brain region, comprising:

an [potassium channel] agonist of a calcium-activated or ATP-sensitive potassium channel, [said potassium channel]the agonist being other than bradykinin or a bradykinin analog; and

instructions for using the [potassium channel] agonist for enhancing the delivery of a medicant to an abnormal brain region by increasing the permeability of a capillary or arteriole delivering blood to cells of the abnormal brain region.

109.(Amended) The kit of Claim 108, wherein the [potassium channel] agonist is NS-1619, 1-EBIO, a guanylyl cyclase activator, a guanylyl cyclase activating protein, minoxidil, pinacidil, cromakalim, or levcromakalim.